

Exploring Potential Energy Hypersurfaces for Triple Symmetric Inversion in 3-Azabicyclo[3.3.1]Nonan-9-One and Its *N*-Methyl Derivative

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ABSTRACT: The potential energy hypersurfaces for the triple inversion, from chair to boat and α to β conformations, are explored theoretically in 3-azabicyclo[3.3.1]nonan-9-one and its *N*-methyl derivative, by using *ab initio* quantum-mechanical calculations. Both compounds are precursors of rigid analogs of the potential GABA_A and GABA_B receptor antagonists. In contrast to results from semiempirical calculations, the chair–chair β conformers are found to be, by far, the most stable structures for both the nonmethylated and *N*-methylated compounds. The inversion barriers are found to be relatively low, so that the conformers could be expected to exist in thermodynamic equilibrium at room temperature. A population analysis reveals, however, that, in the *ab initio* approach, the molecules seem to exist practically only in the chair–chair– β conformation. The theoretical results compare well with the available experimental data. © 1998 John Wiley & Sons, Inc. *J Comput Chem* 19: 1567–1574, 1998

Keywords: polycyclic conformers; GABA rigid precursor analogs; conformer population analysis; comparison between *ab initio*, AM1, and MM2 calculations

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Introduction

In a previous study,¹ an analysis of the hyper-surface corresponding to the triple symmetric inversion in azabicyclo[3.3.1]nonan-9-one and its *N*-methyl derivative (see Fig. 1) was carried out at the AM1 semiempirical level using the MOPAC package. Although the chair-chair preferred conformations compared well with the experimental results,² some doubts remained concerning the orientation of the N—H and N—CH₃ bonds.

As is well known, each of the six-membered rings of these molecules can exist in two forms: chair (C) and boat (B). In addition, the *N*-hydrogen atom (or *N*-methyl group) can adopt two orientations: α or β . As a result, these molecules can exhibit $2^3 = 8$ conformations, namely CC- α , CC- β , CB- α , CB- β , BC- α , BC- β , BB- α , and BB- β , where the first letter is assigned to the piperidine ring and the second to the cyclohexane one.^{3,4} These conformations are energetically separated by certain barriers. Whenever these barriers are low enough, inversion movements may occur from one conformation to another. These intramolecular motions define a potential energy hypersurface.

As far as we are aware, the structures of the 3-azabicyclo[3.3.1]nonane derivatives have been studied only rarely.⁵⁻⁷ The CC conformation has been reported to be the most stable.^{5,6} The structure of these heterocompounds can also be compared with that of bicyclo[3.3.1]nonane,⁷ a compound for which the energy preference between the CC and CB conformations was determined to be 2.3 kcal/mol, by electron diffraction measurements as well as by molecular mechanics calculations.⁸ The energy differences between the CC and CB and BB conformations of this compound were calculated to be 2.3 and 10 kcal/mol, by *ab initio* RHF calculations at the STO-3G level with partial

optimization of the geometry.⁹ Experimental and theoretical studies on diazabicyclononane derivatives were also reported.^{10,11} Very recently the structures of 3-azabicyclo[3.3.1]nonan-9-one and of some related compounds were studied by molecular mechanics and NMR spectroscopy.¹²

The synthesis, as well as the structural and pharmacological properties of some conformationally restricted analogs of the γ -butyric acid (GABA), are presently being considered in a research program devoted to the development of new GABA_A or GABA_B receptor antagonists.^{13,14} In these analogs, the GABA skeleton is mimicked by the 3-azabicyclo[3.3.1]nonane system (see Fig. 1). This work deals with the conformational analysis of 3-azabicyclo[3.3.1]nonan-9-one and its *N*-methyl derivative as precursors of the previous compounds. These molecules present a nonplanar structure. A detailed description of the geometrical features, as well as the energy values of all possible conformers of these molecules, would provide some insight into the structure of the antagonists and hence on their pharmacological actions.

The aim of this study is to analyze the potential energy hypersurfaces of both compounds at the *ab initio* level, determining the critical points, such as minima or first-order saddle points. For this purpose, total molecular energy is determined at each critical point with full optimization of the geometry, and the eigenvalues of the Hessian matrix are assessed.

Method

Ab initio restricted Hartree-Fock calculations, with full optimization of the geometry, were performed using the Gaussian-94 package.¹⁵ Because of the large amount of calculations as well, as the relatively large size of the compounds to be considered in a future study (2,4-diaryl-3-azabicyclo[3.3.1]nonan-9-one), the limited 6-31G** basis set was used for determining the energies and the optimal geometries at the critical points. Berny's optimization as well as the EF option was essential to localize the minima on the potential energy hypersurfaces.

A similar technique, however, did not work to locate the transition structures, TS, along the inter-conversion paths. A generalization of the iterative linear synchronous transit procedure, LST, had to be used.¹⁶ In this procedure, in a first step, an approximate transition structure was located on

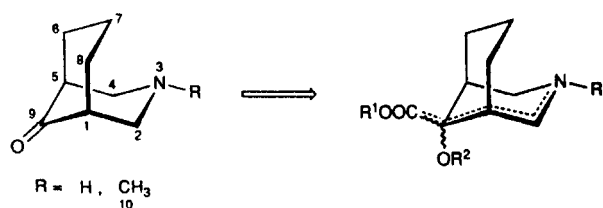


FIGURE 1. Structure of 3-azabicyclo[3.3.1]nonan-9-one and its *N*-methyl derivative. The dashed line shows the molecular superposition of the GABA skeleton, and labeling of the heavy atoms.

restricted hypersurfaces by using the (TS) option. This restricted space, known as the control space, was limited to the internal coordinates mostly affected by the geometrical changes during the inversion (i.e., in the present case, some bending and dihedral angles). In a second step, the rest of the coordinates spanning the complementary space were optimized by using the (EF) option. This procedure was repeated until a mean gradient of 10^{-8} a.u. Å or degrees was reached. Finally, the option, Freq^{15,16} was used to characterize the transition structures; that is, to establish whether they correspond to a critical point of first order or not.

In the present article, the α and β notations are used, as in ref. 1 for the in- and outward *N*-hydrogen (or methyl) orientation with respect to the center of the molecule. As a result, the α structures are always more compact. In particular, the equatorial orientation gives rise to an α structure in the CC and CB conformers, and to a β structure in the BC and BB conformers.

Calculations and Results

CONFORMER DETERMINATION

In general, the semiempirical optimal geometries of the 3-azabicyclo[3.3.1]nonan-9-one compound and its *N*-methyl derivative were used as starting points for the *ab initio* calculations. Although the CC- β preferred conformations for the nonmethylated and *N*-methylated compounds were obtained without any difficulty, this procedure did not work for all conformers. The *N*-methylated compound caused particularly serious difficulties. Therefore, different procedures were used.

The sign of the dihedral angle between the C1C2C4 and C2C4N3 planes, namely C1C2C4N3, of the CC- β structure, was inverted, and the geometrical parameters of the CB- β structure determined. In the same manner, the dihedral angle, C1C8C6C7, and C5C4N3H of the CC- β or CB- β structures, were inverted, and the geometries of the remaining structures optimized. But, even then the α series of the *N*-methyl compound did not converge. Therefore, a second procedure consisting of using the semiempirical geometries at a very low *ab initio* level, and repeating the geometry optimization at an increasing basis set, was attempted.

However, using these procedures, it was not possible to obtain the CC- α conformer of the *N*-methylated compounds, the calculation of which converged to the CC- β conformer. This suggested that the CC- α conformer of the *N*-methylated compound does not exist.

In Table I, the relative energy values for each conformer, with respect to the most stable one (3-azabicyclo[3.3.1]nonan-9-one), as well as the most characteristic optimal dihedral angles, are given.

As expected, the CC conformer is found to be the most stable, followed by the CB, BC, and BB conformers, with energy differences in the β series of 2.32, 4.52, and 10.09 kcal/mol, respectively, in agreement with previous calculations and experimental data on similar molecules^{8,9} as well as with molecular mechanics calculations (MM2).¹²

In contrast to the semiempirical results,¹ the CC- β conformer is found to be more stable than the CC- α one, with an energy difference of 1.77 kcal/mol, in agreement with the MM2 calculations and NMR measurements.¹²

TABLE I.
Relative Energy Values (kcal / mol) with Respect to that of CC- β Conformer (−439.844476 a.u.) and Main Dihedral Angles (Degrees) for Eight Conformers of 3-Azabicyclo[3.3.1]Nonan-9-One.

Conform.	Energy	C5C9C1C8	C1C2C4N3	C1C8C6C7	C5C4N3—H
CC- β	0.0000	64.09	−50.66	+39.90	+178.53
CC- α	1.7728	63.94	−40.25	+39.11	−82.15
CB- β	2.3250	50.81	−55.15	−46.21	+173.68
CB- α	3.7299	59.71	−45.53	−45.84	−75.00
BC- β	4.5227	63.50	+43.67	+45.18	+75.23
BC- α	4.2380	65.38	+54.16	+44.83	−173.56
BB- β	10.0522	50.11	+31.02	−51.69	+67.04
BB- α	10.0880	51.66	+41.03	−51.42	−164.39

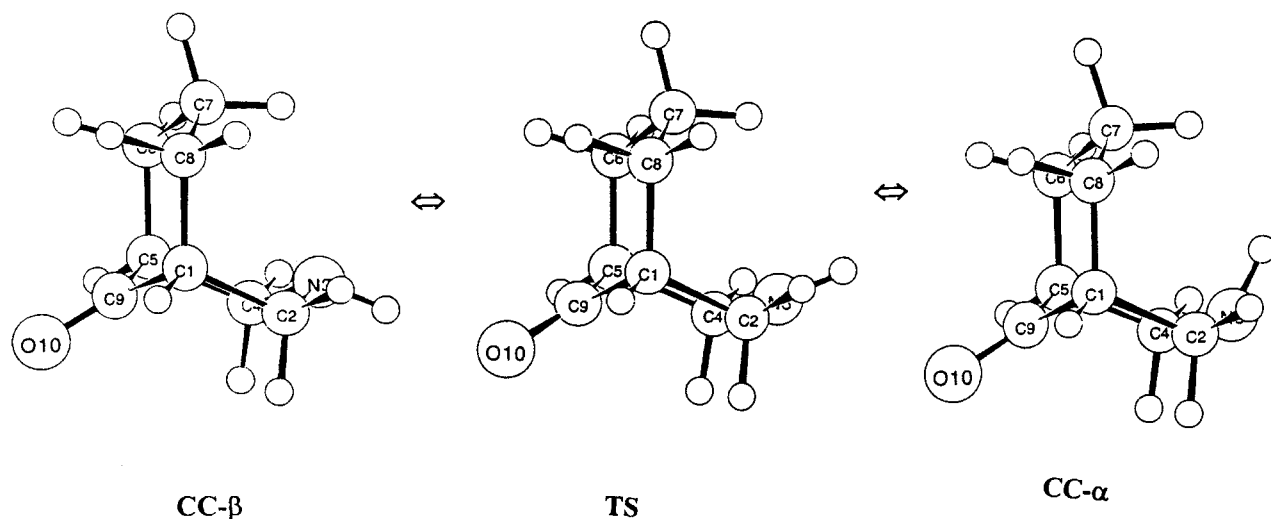


FIGURE 2. A plot of the calculated structures of the lowest conformers of 3-azabicyclo[3.3.1]nonan-9-one, and that of the transition state between them.

It is noticeable that the bicyclic structures of these molecules are found to be bent much more in the present calculation than in the previous semiempirical ones. The semiempirical procedures are indeed known to furnish too-flat structures, but here some dihedral angles between the main planes of the cycles reach values of up to three times greater. The —N—H orientations, however, are essentially the same in both approaches.

In Figure 2, the structures of the most stable conformers, CC- β and CC- α , of 3-azabicyclo[3.3.1]nonan-9-one are represented graphically.

In Table II, the values found for the energy and dihedral angles for the *N*-methylated conformers

are given. Here also, the order of stabilities is $CC > CB > BC > BB$, but only in the β series. The CC- α conformer is probably unstable. The CB- α conformer lies at 10.79 kcal/mol above the CC- β one. In addition, the BC- α and BB- α conformers follow the same trend. The MM2 procedure yields similar results.

From these results, it is clear that the α orientation is not favored, especially in the chair conformation of the piperidine ring. As in the nonmethylated series, the angle values between the main planes of the rings of the *N*-methylated compound are up to three times larger than those found in the semiempirical calculations. This large folding of

TABLE II. Relative Energy Values (kcal/mol) with Respect to that of CC- β Conformer (−478.876088 a.u.) and Main Dihedral Angles (Degrees) for Seven Conformers of *N*-Methyl-3-Azabicyclo[3.3.1]Nonan-9-One.

Conform.	Energy	C5C9C1C8	C1C2C4N3	C1C8C6C7	C5C4N3—CH ₃
CC- β	0.0000	64.54	−48.38	−40.21	+177.98
CC- α	—	—	—	—	—
CB- β	2.6383	60.44	−53.06	−46.01	+173.28
CB- α	10.7906	60.19	−43.38	−45.20	−102.42
BC- β	8.1175	66.77	+44.91	+44.39	+82.87
BC- α	4.1266	65.51	+52.19	+44.70	−173.37
BB- β	13.5357	52.20	+30.51	−50.70	+75.65
BB- α	9.9259	52.00	+39.68	−51.26	−163.77

the molecule gives rise to strong steric effects that could be responsible for the instabilities of the CB- α and especially the CC- α conformer in the *N*-methyl derivative. The —N—CH₃ orientations are essentially the same as in the semiempirical calculations, except for the CB- α conformer, which exhibits a significant deviation.

In Figure 3, the structures of the most stable conformers, CC- β and CB- β , of the IN-methylated compound are represented. No hydrogen bond can be detected between the N-hydrogen and the carbonyl oxygen atoms in the BC and BB conformers, because the N—O distances are too large (3.4–3.5 Å).

The skewness of the molecular rings has been also investigated by calculating the deviations from the planar structure of the four central atoms C1C2C4C5 and C1C8C6C5. Only the BB conformers present appreciable deformations of $\sim 20^\circ$.

Finally, some dihedral angles may be compared with those of a similar compound—3-methyl-2,4-diphenyl-3-azabicyclo[3.3.1]nonan-9-one, measured in the crystal phase by *x*-ray spectroscopy.² This compound possesses the same cyclic structure. In the crystal, however, the unit cell presents two molecules with small structural differences. The relevant angles are given in Table III, together with the theoretical ones for the CC- β and CB- β conformations of both compounds. It is seen that the CC- β conformer dihedral angle values agree reasonably well with those measured experimentally. As a result, the CC- β conformer is, by far, the most probable.

Regarding these dihedral angles, the semiempirical¹ and MM2¹² values are also in agreement with the experimental data, so that this test is not of great significance for comparison of the different approaches.

TRANSITION STRUCTURE DETERMINATION

Transition structures were determined, and in each case the Hessian matrix presented only one negative eigenvalue.

The energy values found for the three lowest transition structures for the inversion in 3-azabicyclo[3.3.1]nonan-9-one, and for the two lowest ones in its *N*-methyl derivative, are shown in Table IV. It can be seen that the barriers are moderately high: CC- $\beta \rightarrow$ CB- β , 7.501; CC- $\beta \rightarrow$ BC- α , 8.562; and CC- $\beta \rightarrow$ CC- α , 4.820 kcal/mol, for the nonmethylated compound. In the same way, the barrier heights are: CC- $\beta \rightarrow$ CB- β , 7.689; and CC- $\beta \rightarrow$ BC- α , 12.267 kcal/mol for the *N*-methyl derivative. As a result, the conformers of these molecules may be expected to be in thermodynamic equilibrium at ordinary temperatures. The CC- $\beta \rightarrow$ CC- α and CC- $\beta \rightarrow$ CB- β intramolecular conversion are illustrated in Figures 2 and 3 for the nonmethylated and *N*-methylated compounds, respectively.

In Table IV, the most characteristic dihedral angles found for the transition structures are also given, as well as the values of the negative frequency. During inversion CC- $\beta \rightarrow$ CB- β of the nonmethylated compound, the C1C8C6C7 angle is

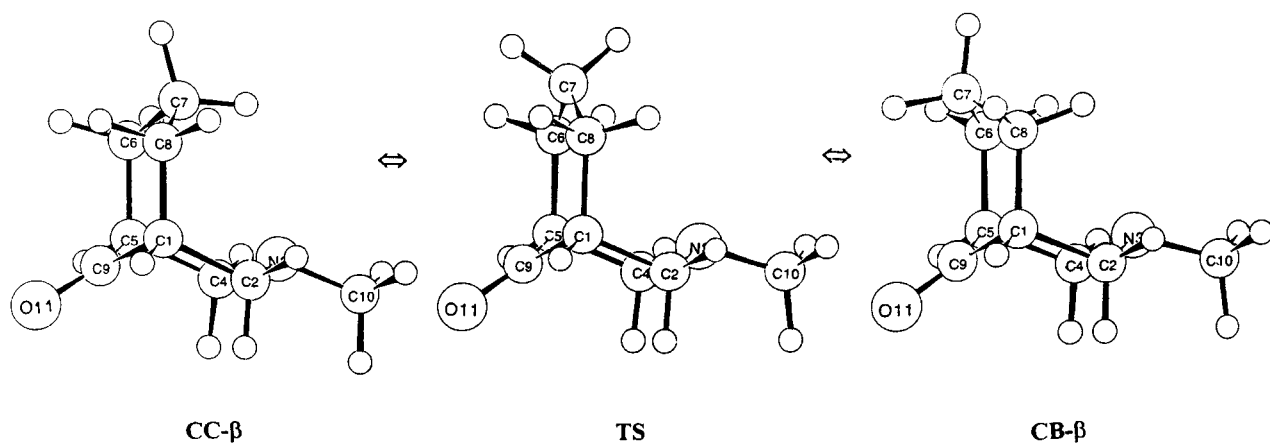


FIGURE 3. A plot of the calculated structures of the lowest conformers of 3-methyl-3-azabicyclo[3.3.1]nonan-9-one, and that of the transition state between them.

TABLE III.
Selected Dihedral Angles (Degrees) as Determined by X-Ray Spectroscopy in 3-methyl-2,4-diphenyl-3-azabicyclo[3.3.1]Nonan-9-One.

Conform.	R=H		R=CH ₃		Exp.
	CC-β	CB-β	CC-β	CB-β	
N3C2C1C9	56.01	58.17	55.69	58.07	52.0; 53.5
C7C6C5C9	53.41	3.24	53.87	3.72	52.7; 54.1
C1C2N3C4	-55.97	-60.55	-54.00	-58.81	-47.6; -47.7
C1C8C7C6	44.67	-51.20	44.95	-50.94	48.6; 48.7

seen to vary from +39.90° in the CC conformer, through -5.77° in the transition structure to -46.21° in the CB conformer. On the contrary, the C1C2C4N3 and C5C4N3-H angles adopt roughly similar values during inversion: -50.66° and 178.53° in the CC conformer; -56.64° and 173.29° in the transition structure; and -55.15° and 173.68° in the CB conformer, respectively. As a result, the C1C8C6C7 angle is seen to vary nearly independently of the other two, with the CC-β → CB-β inversion.

In the same way, considering the inversion CC-β → BC-β in the nonmethylated compound, the C1C2C4N3 angle is seen to vary from -50.66° in the CC conformer, through 40.85° in the transition structure, and 54.16° in the CB conformer. In contrast, the C1C8C6C7 angle adopts similar values during the inversion: +39.90°, +46.52°, +44.83° in the CC conformer, transition structure, and BC conformer, respectively, whereas the C5C4N3—H angle adopts values of 178.53°, 129.17°, and -173.56°. As a result, the C1C2C4N3 angle is seen to vary nearly independently of the C1C8C6C7

angle, but in a coupled way with the C5C4N3—H angle.

In a similar way, regarding the inversion CC-β → CC-α in the same compound, the C2C4N3—H angle is seen to vary widely from 178.53° in the β conformer, through 128.09° in the transition structure, and -82.15° in the α conformer. In contrast, the C1C8C6C7 angle is practically constant during the inversion (39.90°, 41.44°, 39.11°), whereas the C1C2C4N3 angle varies somewhat (-50.66°, -42.16°, -40.25°). As a result, the C5C4N3—H angle inversion is seen to be a synchronic process in which the C1C2C4N3 angle varies continuously through the transition structure to reach the α conformer.

Identical considerations may be deduced from Tables II and V in the case of the N-methylated compound, so that the same conclusions hold. These couplings can also be detected in the transition vectors corresponding to the negative eigenvalue of the Hessian matrix.

Finally, considerations on the N—H orientation in the CC-α conformer (Fig. 2) and on that of

TABLE IV.
Energy Values (kcal / mol) for Some of the Lowest Transition Structures on the Hypersurfaces of 3-Azabicyclo[3.3.1]Nonan-9-one and Its N-Methyl Derivative as Well as Their Main Dihedral Angles (Degrees) and Negative Frequencies (cm⁻¹).

	Trans. struct.	Energy	C1C2C4N3	C1C8C6C7	C5C4N3-R	Freq.
R=H	CC-β → CB-β	7.5007	-56.64	-5.77	173.29	-753.79
	CC-β → BC-α	8.5620	+40.85	+46.52	129.17	-640.90
	CC-β → CC-α	4.8192	-42.16	+41.44	128.09	-620.93
R=CH ₃	CC-β → CB-β	7.6889	-54.54	-5.92	172.66	-262.84
	CC-β → BC-α	12.2673	-46.70	+44.92	124.23	-189.85

TABLE V. Populations of the Eight Conformers Calculated at 300 K for 3-Azabicyclo[3.3.1]Nonan-9-One (—N—H) and Its *N*-Methyl Derivative (—N—CH₃) at the AM1 Semiempirical, *Ab Initio*, and MM2 Molecular Mechanics Levels.

Conformers	Semiempirical		<i>Ab initio</i>		MM2	
	—N—H	—N—CH ₃	—N—H	—N—CH ₃	—N—H	—N—CH ₃
CC- β	0.0043	0.4814	0.9292	0.9868	0.97	0.99
CC- α	0.7372	0.0377	0.0484	—	0.02	0.00
CB- β	0.0006	0.0671	0.0193	0.0215	0.01	0.01
CB- α	0.2336	0.1896	0.0018	0.0000	0.00	0.00
BC- β	0.0239	0.1946	0.0005	0.0000	0.00	0.00
BC- α	0.0002	0.0285	0.0008	0.0010	0.00	0.00
BB- β	0.0001	0.0010	0.0000	0.0000	0.00	0.00
BB- α	0.0000	0.0001	0.0000	0.0000	0.00	0.00

N—CH₃ in the CB- β conformer (Fig. 3) can likely explain why the CC- α conformer does not exist in *N*-methylated compounds.

In Table V, the Boltzmann probability distributions, calculated at 27°C, and at the *ab initio*, semiempirical,¹ and MM2 levels,¹² are given for the eight conformers of both compounds under study. In the *ab initio* and MM2 calculations, the CC- β conformers are seen to be, by far, the most probable ones for both derivatives. In contrast, the semiempirical calculations predict a very different population distribution, with the CC- α conformer of the nonmethylated derivative being the most probable, and the CC- β conformer of the *N*-methyl derivative only slightly preferred.

Conclusions

In this study, *ab initio* calculations performed at the RHF level with the 6-31G** basis set satisfactorily reproduced the relative energy values of the different conformers of 3-azabicyclo[3.3.1]nonan-9-one and its *N*-methyl derivative. The *ab initio* calculations predicted that the chair-chair conformers were the most stable, followed by chair-boat, boat-chair, and boat-boat, in accordance with experiment and AM1 and MM2 calculations.

The *ab initio* calculations predicted structures twice more folded than those obtained in the semiempirical approach. The N-R orientations are similar to those in the semiempirical calculations.

In contrast to the semiempirical results, the *ab initio* calculations predicted that the β conformers were generally more stable than the α ones in both series, with CC- α likely being the least stable.

The inversion barrier heights between the lowest conformers were found to be sufficiently small in both series, so that the conformers can exist in thermodynamic equilibrium at normal temperature. The population distributions obtained at the *ab initio* levels were practically monokonformational, in contrast to the semiempirical results, but in agreement with the MM2 findings.

As a result, the semiempirical procedures have to be used with special caution in population analyses of polycyclic molecules, especially in those with a nitrogen atom in their rings.

C1C8C6C7 angle inversion seems to be relatively independent of the other two inversion angles. In contrast, the C1C2C4N3 and C5C4N3—R angle inversion appear to be strongly coupled in both series.

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